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Catalytic synthesis of enantiopure mixed diacylglycerols – synthesis of a major *M. tuberculosis* phospholipid and platelet activating factor†

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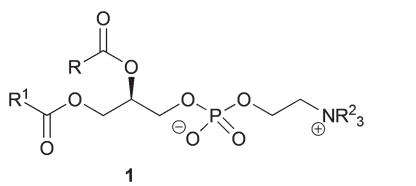
An efficient catalytic one-pot synthesis of TBDMS-protected diacylglycerols has been developed, starting from enantiopure glycidol. Subsequent migration-free deprotection leads to stereo- and regiochemically pure diacylglycerols. This novel strategy has been applied to the synthesis of a major *Mycobacterium tuberculosis* phospholipid, its desmethyl analogue, and platelet activating factor.

Diacylglycerols and diacyl glycerophospholipids (Fig. 1) are compounds with enormous significance for living organisms.[1–3] Involved in numerous physiological processes, these are the major components of cell membranes, and several diacyl glycerolphospholipids have therapeutic applications.[4] Natural phospholipids mostly contain a polar headgroup, either a phosphatidylethanolamine or a phosphatidylcholine, and two different acyl chains. The differences in length of the acyl chains, together with the number and position of unsaturations within the chains, explain the huge variability in their structure. On the other hand, the similarity in physical properties of diacyl glycerolphospholipids often precludes their isolation in pure form from natural sources, and puts strict requirements on regio- and stereoselectivity in their chemical synthesis.

Therefore, diacylglycerols bearing two different acyl residues are challenging synthetic targets despite their apparent structural simplicity. Next to regioselective esterification of the glycerol unit, the tendency of a 1,2-diacylglycerol **2** to undergo acyl shift to the corresponding 1,3-diacylglycerol **3** is a challenging problem[5,6] (Fig. 2). This acyl shift is catalysed by traces of (Lewis) acids and bases and also occurs on chromatography stationary phases like silica gel and aluminium oxide, leading to decreased yields and tedious purification.



1

R =/= R^1
R^2 = H : phosphatidylethanolamine
R^2= Me : phosphatidylcholine

Fig. 1 Mixed diacyl glycerolphospholipids.

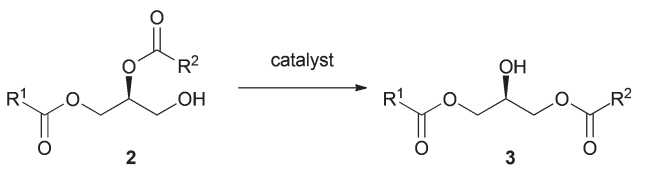


Fig. 2 1,2- to 1,3-Acyl shift.

Over the years, the synthesis of diacylglycerols and phospholipids has attracted significant attention in organic chemistry and several routes have been developed. Starting from enantiopure *p*-methoxybenzyl ether-protected glycerol, Martin *et al.*[7] obtained mixed diacyl glycerolphospholipids with a PE headgroup in a sequence of 8 steps and an overall 52% yield. In the approach of D'Arrigo *et al.*,[8] stoichiometric dibutyltin oxide is used for the regioselective acylation of the terminal hydroxy group of glycerophosphocholine. In this way, various mixed diacylglycerols were obtained in modest to high yields (25–80%). Furthermore, a chiral pool strategy has been presented by Massing and Eibl[9] using D-mannitol to prepare several ether-based lipids like platelet activating factor (PAF). In a different approach, Stawinski and Stamatov[10,11] used halohydrins derived from enantiomerically pure silyl protected glycidols. A three-fold excess of the fatty acids is employed in this case. Yet another, efficient, strategy has been presented by Gras and Bonfanti[12] in which they used 5-hydroxy-1,3-dioxane (formaldehyde protected glycerol) to synthesize selectively mixed 1,2-diacylglycerols. A drawback of this approach is that

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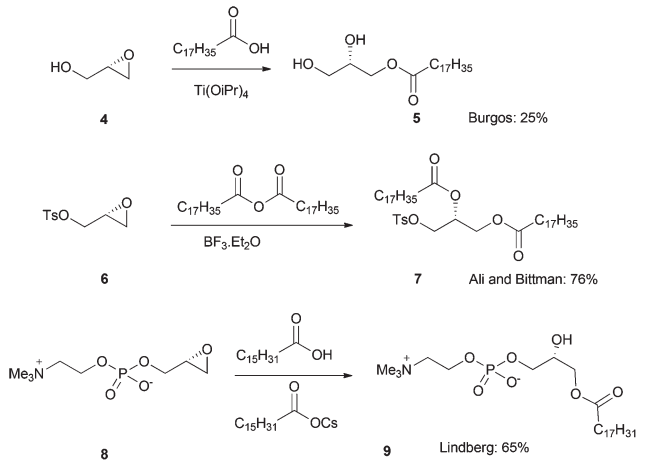


Scheme 1 Phospholipid syntheses with epoxide ring opening as the key step.

the products are racemic. Finally, 1,2-diacylglycerols can be prepared by chemo-enzymatic methods presented by Guanti *et al.*[13] Starting from racemic solketal ((2,2-dimethyl-1,3-dioxolan-4-yl)methanol) by treatment with Amano P protease, the desired 1,2-dipalmitoyl-*sn*-glycerol is obtained in 55% yield.

Overall, the described approaches circumvent the issues of regioselective acylation and acyl shift, primarily by protecting group installation and removal, or alternatively by kinetic resolution. It has however been realized that regioselective ring opening of glycidol (2,3-epoxy-1-propanol) or its derivatives is in principle an attractive and atom economical alternative. This strategy has been pursued in several ways but not without difficulty. Burgos *et al.*[14] (Scheme 1) have described an approach applying two equiv. of fatty acid and a super-stoichiometric amount of $Ti(O^iPr)_4$. The desired product **5** was isolated in only 25% yield, with some loss of optical purity.

The approach of Ali and Bittman[15] uses $BF_3{\cdot}OEt_2$-mediated ring-opening of tosylated glycidol **6**. As a fatty acid anhydride is applied, this method is limited to 1,2-diacylglycerols containing two identical acyl chains.

A third approach based on epoxide ring opening has been reported by Lindberg *et al.*[16] Heating glycidyl phosphate **8** with a mixture of a fatty acid and its corresponding cesium salt (2 equiv. in total) in DMF affords the desired *lyso* lipid **9** in moderate 65% yield (Scheme 1).

In connection with our research on mycobacterial[17] and archaea[18] lipids, we realized that a general, efficient, and preferably catalytic approach to enantiopure mixed diacylglycerols would be highly desirable. Conceptually, the use of the well-known cobalt(salen) **C1**[19–21] catalyst for the highly enantioselective hydrolytic kinetic resolution of substituted glycidols would be very attractive, in particular if only 1 equiv. of a fatty acid as the nucleophile would suffice. This cobalt(salen) catalyst **C1**, developed by the Jacobsen group, has proven to be very efficient in the hydrolytic kinetic resolution of terminal epoxides and the desymmetrization of *meso* epoxides[21] with carboxylic acids. Its utilisation in the terminal epoxide ring opening with carboxylic acids has however not been described.

Both **C1** and TBDMS protected glycidol **10** are commercially available, and we commenced by performing the epoxide ring opening reaction under modified Jacobsen conditions. The reaction was carried out neat, *e.g.* solvent-free, with 1 mol% of catalyst, enantiopure TBDMS protected glycidol, 1 equiv. of Hünig's base and 1 equiv. of octanoic acid. To our delight, this afforded monoacyl glycerol **11** as a single regioisomer in virtually quantitative yield as confirmed by ^{1}H-NMR, ^{13}C-NMR and GC-MS. As **11** was obtained in high purity and only 1 equiv. of fatty acid was employed, we combined the ring opening of TBDMS-glycidol **10** with subsequent DCC/DMAP esterification of the resulting secondary alcohol with a second fatty acid[22] (Scheme 3). This one-pot procedure gave the corresponding TBDMS-protected 1,2-diacylglycerol **12**. When the reaction reached full conversion, the crude mixture was directly purified over a silica gel column without any workup affording **12** in an excellent 92% yield over two steps (Scheme 3)!

It turned out that the reaction is readily scaled-up. At 5 mmol scale (in epoxide **10** and stearic acid), 91% yield – 3.2 g – isolated product was obtained. To test the tolerance of the cobalt catalyst to the presence of a double bond in the fatty acid applied for the ring opening, also TBDMS protected 1,2-diacylglycerol carrying an oleic acid residue on the primary and a palmitic acid residue on the secondary position was prepared in the same way. The isolated yield over 2 steps was 82%, slightly diminished compared to the previous synthesis with two saturated fatty acid residues but still very high (see ESI†).

Desilylation of the protected 1,2-diacylglycerol **12** is a challenge, as has already been recognized.[23–26] Acyl migration during deprotection of protected 1,2-diacylglycerols is a long-standing problem, especially since the rearranged 1,3-diacylglycerol is very difficult to separate from the desired product. We examined a wide variety of conventional deprotection conditions including TBAF and TFA,[27] but in all cases substantial migration was observed before reaching full conversion. Conditions that applied Lewis or Brønsted acids in only catalytic amounts[28] gave similar results at best. Finally, we found that using a small excess of boron trifluoride (BF_3, either as its etherate or as acetonitrile complex) in CH_2Cl_2 at 0 °C cleaves the TBDMS group with only minimal migration (<5%, TLC, NMR[29]) within 5 min. The reaction has to be closely monitored (by TLC) and upon full conversion it has to be quenched immediately. To avoid any migration during work-up, quenching was carried out with chilled phosphate buffer (1 M, pH = 7). The so-obtained 1,2-diacylglycerol was isolated in an excellent 96% yield and used without further purification.

To prepare 1,2-diacyl phosphatidylethanolamine **14**, the protected phosphoethanolamine was introduced by the phosphoramidite coupling/oxidation methodology.[30,31] This method is widely used in solid-phase DNA synthesis, and was selected because the mild reaction conditions and short reaction times minimize the possibility of acyl migration. Full conversion was achieved within 15 min using 4,5-dicyanoimidazole as the activator. The reaction turned out to be very clean and product **13** was obtained in 85% yield. Finally,

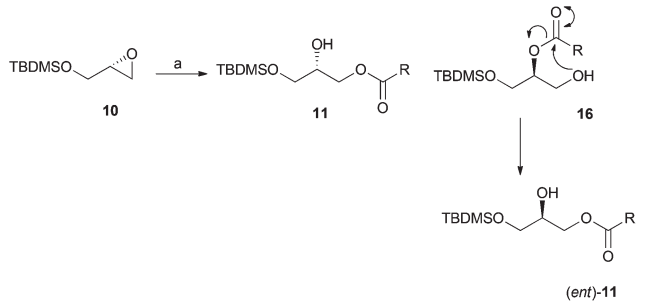
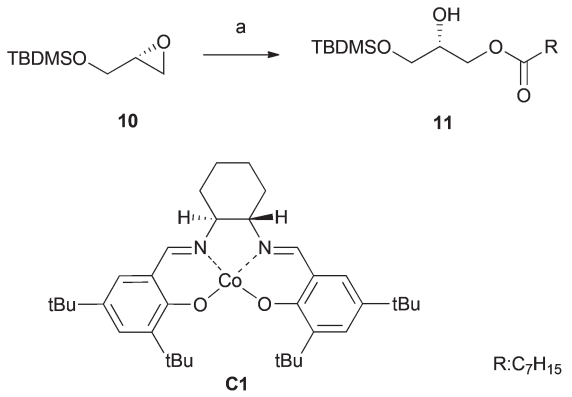


Fig. 3 Possible decrease of the optical purity as a result of low regioselectivity.

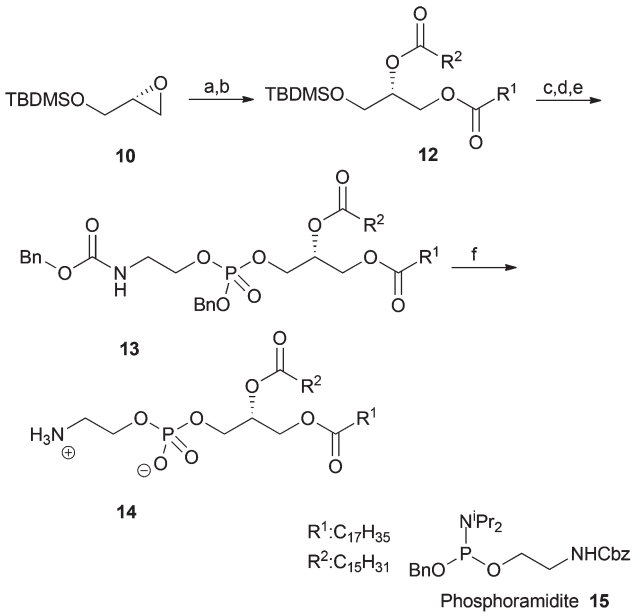
protecting groups were removed by hydrogenolysis over Pd/C. This led after purification over silica-gel to the desired 1,2-diacyl phosphatidylethanolamine.

To investigate whether the optical purity of starting glycidol **10** erodes during the ring opening step, we employed Mosher's ester analysis.[32,33] It is important to point out the possibility of an acyl shift similar to the one depicted in Fig. 3. If the epoxide opening displays a low selectivity for the primary position (affording **16** instead of **11**), a subsequent intramolecular acyl shift would lower the enantiomeric excess of **11**.

Although Mosher's ester analysis is an often used method in the field of phospholipids,[14–16,34,35] the reported ^{1}H and ^{18}F NMR shifts are in some cases contradictory. Furthermore, we encountered incomplete conversion of the starting material which, together with attempts to purify the diastereomeric diacylglycerols, can lead to an undesired kinetic resolution. To circumvent these issues, HPLC with a chiral stationary phase was applied to analyse the optical purity after the ring opening step. To this end, the reaction was performed with the closely related TBDPS-glycidyl ether[36] (see ESI†). Ring opening proceeded smoothly by applying identical reaction conditions (Scheme 2) and the resulting protected monoacylglycerol was analysed without any further sample manipulation. To our delight, absolutely no decrease of the optical purity was observed during this step. It is therefore safe to conclude that the reaction occurs regio-specifically on the terminal position of the epoxide.



Scheme 2 *Reagents and conditions*: (a) octanoic acid (1 equiv.), Hünig's base (1 equiv.), **C1** (1 mol%), 16 h, 21 °C.

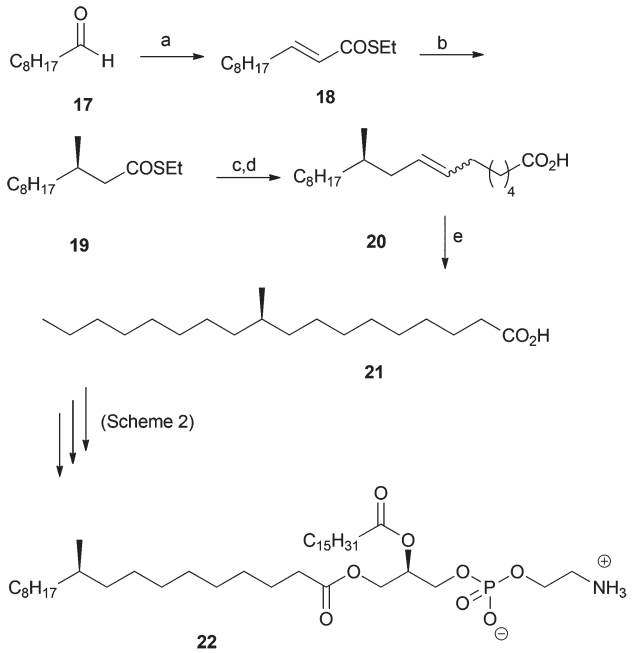


Scheme 3 *Reagents and conditions*: (a) $C_{17}H_{35}CO_2H$ (1 eq.), DIPEA (1 eq.), Co-(salen) cat. (1 mol%), 21 °C, 16 h; (b) $C_{15}H_{31}CO_2H$ (1.2 eq.), DCC (1.1 eq.), DMAP (10 mol%), heptane, 21 °C, 16 h; (c) $BF_3{\cdot}CH_3CN$ (1 eq.), CH_2Cl_2, 21 °C, 5 min; (d) phosphoramidite (1.2 eq.), 4,5-dicyanoimidazole (1 eq.), CH_2Cl_2 15 min; (e) *t*-BuOOH (3 eq.), 10 min; (f) Pd/C (5 mol%), MeOH–HCO_2H–THF, H_2, 21 °C.

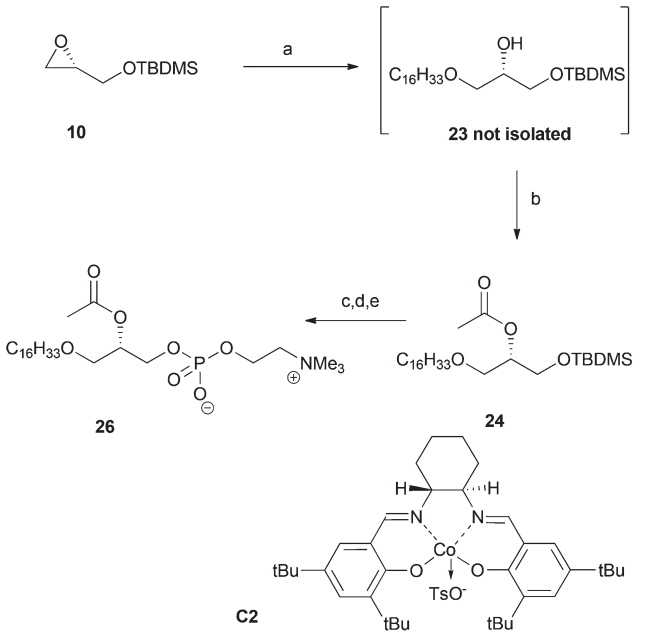
This novel and efficient methodology was subsequently applied to the synthesis of a major phospholipid (**22**) from *M. tuberculosis*. Mycobacteria are known to protect themselves with a remarkably thick cell wall containing various multi-methyl-branched lipids. Also the plasma membrane contains a major phosphatidylethanolamine (PE) based phospholipid bearing a methyl-branched fatty acid residue. This fatty acid, (*R*)-tuberculostearic acid **21**, is attached to the *sn1* position[37] of the glycerol.[17,38] The limited accessibility and the incomplete understanding of the behaviour of phospholipids bearing methyl branched fatty acids made this lipid **22** (Scheme 4) an interesting target for our methodology, all the more so because only 1 equiv. of precious tuberculostearic acid is employed.

To date, several routes to racemic[39] and enantiomerically pure[17,40–44] (*R*)-tuberculostearic acid **21** have been described. In the most recent synthesis, we used[17] copper catalyzed enantioselective conjugate addition of methylmagnesium bromide for the introduction of the stereogenic center. With this reaction as the key step we envisioned to make the synthesis even shorter and more efficient.

In the event, (*R*)-tuberculostearic acid was prepared in a linear five step synthesis starting from commercially available nonanal **17**. Unsaturated thioester **18** was prepared by treatment of **17** with a stabilized Wittig reagent[45] (Scheme 5) using "on water" conditions. Product **18** was isolated in 92% yield as a single *E* isomer. To install the methyl branch, **18** served as the substrate for a copper/Josiphos[46,47] catalysed conjugate addition of MeMgBr. This afforded the branched product **19** in 93% yield and 90% ee.



Scheme 4 *Reagents and conditions*: (a) $Ph_3P{=}CHC(O)SEt$ (1.5 eq.), LiCl (10 mol%), H_2O, 21 °C, 16 h; (b) Cu[*S*,*R*]-Josiphos (1 mol%), MeMgBr (1.5 eq.), MTBE, −78 °C, 14 h; (c) DIBAL-H, CH_2Cl_2, −50 °C, 2 h; (d) $Br^-Ph_3P^+C_6H_{12}CO_2H$ (1.5 eq.), LiHMDS (2.8 eq.), THF, 21 °C, 2 h; (e) flavin catalyst (10 mol%), $NH_2NH_2{\cdot}H_2O$ (25 eq.), O_2 (balloon), 21 °C.



Scheme 5 *Reagents and conditions*: (a) **10** (1 eq.), hexadecanol (0.6 eq.), **C2** (2 mol%), THF, 21 °C, 3 d; (b) Ac_2O (2.5 eq.), Et_3N (2.5 eq.), DMAP (10 mol%), CH_2Cl_2, 21 °C, 16 h; (c) $BF_3{\cdot}CH_3CN$ (1.1 eq.), CH_2Cl_2, 0 °C, 20 min; (d) 2-chloro-1,3,2-dioxaphospholane 2-oxide (4 eq.), Hünig's base (4 eq.), CH_2Cl_2, 0 °C, 16 h; (e) NMe_3 (1.5 eq.), TMSOTf (2 eq.), CH_2Cl_2.

Thioester **19** was reduced to the corresponding aldehyde with DIBAL and elongated using the appropriate acid-functionalized Wittig reagent. To avoid any racemisation of the methyl-branched stereocenter in **20**, the double bond was reduced with diimide, produced *in situ* by a flavin-based catalyst for the controlled oxidation of hydrazine.[48,49] In this way, (*R*)-tuberculostearic acid **21** was prepared in 5 steps and 63% overall yield, the shortest route to date.

The so-obtained (*R*)-tuberculostearic acid **21** was subsequently converted into the *M. tuberculosis* 1,2-diacyl phosphatidylethanolamine following the sequence described in Scheme 2 in 64% overall yield.

To further broaden the scope of our methodology, we aimed at the synthesis of the well-known platelet-activating factor (PAF). This mixed ether/ester type phosphatidylcholine lipid effects the aggregation of platelets and has a messenger function in processes like glycogen degradation, reproduction, brain function and blood circulation. To date, several syntheses of PAF have been reported.[9,50–55] Initially, though, we observed very little conversion applying the conditions for epoxide opening by acids (*vide infra*). This is probably due to the poor nucleophilicity of the hexadecanol. By applying the more electrophilic cobalt^{III}[salen]OTs catalyst, which we[18] and others[56] found to be more efficient in epoxide ring opening with alcohols as nucleophiles (Scheme 5), full conversion of the hexadecanol was achieved. To our delight, the reaction proceeds in the same clean manner, affording ring-opened product **23** as a single regioisomer. **23** was esterified in the same reaction vessel with an excess of acetic anhydride under basic conditions and in the presence of DMAP. PAF precursor **24** was isolated in 68% yield over two steps. It is important to note that ring opening requires only 2 mol% of the catalyst. The subsequent desilylation was a serious test for our methodology. It was found that 1.1 equivalents of the $BF_3{\cdot}CH_3CN$ complex at 0 °C cleaves the protecting group in 20 min without any migration detected by NMR (see ESI†). The phosphatidylcholine headgroup was further introduced by an established two step procedure. First, the free hydroxyl group was treated with an excess of 2-chloro-1,3,2-dioxaphospholane 2-oxide which was subsequently opened by NMe_3 in the presence of TMSOTf as a Lewis acid catalyst[57] (Scheme 5). Platelet-activating factor was isolated after column chromatography in 68% yield over three steps.·Overall, PAF was synthesized in a five step sequence starting from commercially available enantiopure glycidol in 46% yield. In the past, similar routes were abandoned because of the acetyl migration.

Conclusions

A one-pot synthesis of enantiopure mixed diacylglycerols **12** has been developed, starting from TBDMS-protected glycidol. The protocol is experimentally straightforward, requires only equimolar amounts of fatty acids and provides the TBDMS protected diacylglycerols in excellent yields. Using the more electrophilic cobalt^{III}[salen]OTs catalyst we were able to extend our methodology to the synthesis of mixed ether/ester type

phospholipids. The longstanding problem of acyl migration upon deprotection of diacylglycerols was solved with the combination of a TBDMS protecting group and a BF_3-mediated cleavage protocol. An improved synthesis of (*R*)-tuberculostearic acid **21** was developed and used in the preparation of the major *M. tuberculosis* phospholipid **22**.

Experimental section

(*E*)-*S*-Ethyl undec-2-enethioate (18)

To a suspension of $Ph_3P{=}CHC(O)SEt$ (5.10 g, 14.0 mmol) in water (10 ml), lithium chloride (85 mg, 2.0 mmol) and nonanal (1.7 ml, 10 mmol) were added. The mixture was subsequently stirred for 18 h. Subsequently, the water was evaporated, the residue was dissolved in CH_2Cl_2 (30 ml) and adsorbed on silica. After evaporation, the residue was placed on top of the column (dry loading) and chromatographed using 5% toluene in pentane.

The desired (*E*)-*S*-ethyl undec-2-enethioate[58] (**18**, 2.11 g, 9.24 mmol, 92%) was obtained as a colorless thick liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (dt, J = 15.5, 7.0 Hz, 1H), 6.08 (d, J = 15.5 Hz, 1H), 2.93 (q, J = 7.4 Hz, 2H), 2.17 (ddd, J = 14.7, 7.3, 1.5 Hz, 2H), 1.50–1.36 (m, 3H), 1.26 (m, 12H), 0.87 (t, J = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.11, 145.41, 128.63, 32.14, 31.80, 29.3, 29.14 (2×), 27.97, 22.99, 22.62, 14.80 (–),[59] 14.05 (–).

HRMS: calculated for $C_{13}H_{25}OS$ [M + 1]: 229.162, found 229.162.

(*R*)-*S*-Ethyl 3-methylundecanethioate (19). (R,S_{Fe})-Josiphos·EtOH adduct (49 mg, 83 μmol, 1.65 mol%) and CuBr·Me_2S (15.0 mg, 75 μmol, 1.5 mol%) were stirred in freshly distilled MTBE (45 ml) until homogeneous (approx. 20 min). The mixture was cooled to −78 °C (cryostat) and a solution of MeMgBr in Et_2O (from Acros, 3 M, 2.0 ml, 7.5 mmol, 1.2 eq.) was added dropwise. After stirring for 10 min, a solution of **18** (1.14 g, 5 mmol) in MTBE (5 ml) was added over 3 h by a syringe pump. After addition, the mixture was stirred for an additional 16 h. Then, EtOH (5 ml) was added and the flask was removed from the cooling bath. An aqueous solution of NH_4Cl (1 M, 20 ml) was added and the mixture was stirred for 20 min at rt. The resulting solution was transferred to a separatory funnel and the aqueous layer was diluted with water (30 ml). Layers were separated, the aqueous layer was extracted with Et_2O (3 × 15 ml), and the combined organic layers were washed with brine (50 ml), dried over $MgSO_4$ and evaporated. The crude residue (a yellow-orange liquid) was purified by column chromatography (SiO_2, 1/50 Et_2O–pentane) to afford **19** (1.15 g, 94%) as a thick colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (q, J = 7.4 Hz, 3H), 2.52 (dd, J = 14.4, 6.0 Hz, 1H), 2.33 (dd, J = 14.4, 8.1 Hz, 1H), 2.00 (broad s, J = 5.9 Hz, 1H), 1.33–1.17 (m, 17H), 0.92 (d, J = 6.7 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ 199.32, 51.40, 36.61, 31.86, 31.06, 29.69 (–), 29.55, 29.27, 26.82, 23.23, 22.65, 19.51 (–), 14.78 (–), 14.08 (–).

HRMS calculated for $C_{14}H_{29}OS$ [M + 1]: 245.193 found 245.193.

$[\alpha]_D$ = +3.32° (c = 1.02, $CHCl_3$).

The enantiomeric excess was determined on the corresponding carbamate, obtained by $LiAlH_4$ reduction, treatment with phosgene and treatment with (*S*)-(–)-1-(1-naphthyl)-ethylamine.

Chiracel OD-H, flow = 1 ml min^{-1}, t_{minor} = 11.4 min, t_{major} = 12.4 min, er = 95 : 5.

(*R*)-3-Methylundecanal

This compound was used without purification. One time, isolation was performed in order to confirm its absolute configuration.

To a solution of (*R*)-*S*-ethyl 3-methyl undecathioate (978 mg, 4 mmol) in dry CH_2Cl_2 (23 ml), cooled to −78 °C (EtOH/dry ice), a solution of DIBAL-H in CH_2Cl_2 (1 M, 5.2 ml, 1.3 eq.) was added. The mixture was stirred until complete consumption of the starting material (approx. 2 h, TLC). The solution was poured into saturated Rochelle salt and stirred until phases separated (overnight). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 ml), the combined organic layers were washed with brine, dried over $MgSO_4$ and carefully evaporated. The residual colorless liquid was purified by column chromatography (Et_2O–pentane = 1 : 50) to afford 737 mg (94%) of a pleasantly smelling colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89–9.64 (m, 1H), 2.39 (ddd, J = 16.0, 5.7, 2.1 Hz, 1H), 2.22 (ddd, J = 16.0, 7.8, 2.6 Hz, 1H), 2.04 (d, J = 6.7 Hz, 1H), 1.28 (d, J = 15.0 Hz, 13H), 0.96 (d, J = 6.7 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.15, 41.58, 36.64, 31.87, 30.12 (–), 29.69, 29.55, 29.27, 26.86, 22.65, 19.66 (–), 14.07 (–).

$[\alpha]_D$ = +10.3 (c = 0.25, hexanes).

HRMS: calculated for $C_{12}H_{25}O$ [M + 1] 185.191, found 185.193.

(*R*)-10-Methyloctadec-7-enoic acid (20 – mixture of *E*/*Z* isomers)

To a vigorously stirred suspension of 7-(bromotriphenylphosphoranyl)heptanoic acid (2.51 g, 1.4 eq.) in THF (4 ml) at 21 °C, a solution of LiHMDS (1 M, 10.6 ml, 2.8 eq.) was added dropwise. After 30 min of stirring, (*R*)-3-methylundecanal (0.7 g, 3.80 mmol) in a small amount of THF (1 ml) was added dropwise over 5 min. The resulting reaction mixture was stirred until the solution remained pale yellow (3 h), and then HCl (1 M, aqueous) was added until the pH reached 1. The mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 25 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated. The residual thick colorless liquid was purified by column chromatography (silica, Et_2O–pentane = 1 : 4 + 1% formic acid) to afford 890 mg (79%) of **20** as a mixture of *E* and *Z* isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53–5.23 (m, 2H), 2.35 (t, J = 7.5 Hz, 2H), 2.12–1.92 (m, 2H), 1.65 (dd, J = 9.9, 5.0 Hz, 1H), 1.53–1.01 (m, 23H), 0.86 (dt, J = 14.7, 7.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.49, 130.11, 128.81, 36.70, 34.52, 33.40, 31.91, 29.96 (–), 29.66, 29.34, 29.30, 28.72, 27.17, 27.07, 24.58, 22.67, 19.58 (–), 14.10 (–).

(*R*)-Tuberculostearic acid (21). To a solution of (*E*)- and (*Z*)-(*R*)-10-methyloctadec-7-enoic acid (741 mg, 2.5 mmol) and hydrazine hydrate (2.5 ml, 52.5 mmol) under an O_2 atmosphere, riboflavin catalyst (47.5 mg, 0.125 mmol) was added in one portion. The mixture turned from red to yellow and the reaction was stirred for 24 h at ambient temperature (21 °C). After complete conversion of the starting material, the solution was acidified with concentrated HCl to pH = 1 and extracted with Et_2O (3 × 50 ml). The combined organic layers were dried over $MgSO_4$ and evaporated. The residual yellow thick liquid was purified using column chromatography to afford 724 mg of (*R*)-tuberculostearic acid (97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (t, J = 7.5 Hz, 2H), 1.63 (dt, J = 15.0, 7.5 Hz, 2H), 1.42–1.00 (m, 27H), 0.88 (t, J = 6.9 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.82, 37.08, 37.05, 34.06, 32.73 (–), 31.91, 30.02, 29.92, 29.68, 29.45, 29.35, 29.23, 29.05, 27.07, 27.02, 24.65, 22.67, 19.69 (–), 14.09 (–).

HRMS: calculated for $C_{19}H_{38}O$ [M − 1]: 282.291, found 282.279.

$[\alpha]_D$ = −0.2 (c = +3.1, $CHCl_3$).

One-pot synthesis of protected diacylglycerols

(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-(palmitoyloxy)propyl stearate (12). Stearic acid (1.42 g, 5 mmol, 1 eq.) and Co[salen] (30 mg, 50 μmol, l mol%) were suspended in a small amount of ether (1 ml) and stirred under an oxygen atmosphere for 15 min at 21 °C. The solvent was evaporated and Hünig's base (873 μl, 5 mmol, 1 eq.) was added. After 5 min of stirring, (*R*)-TBDMS-glycidyl ether (1 ml, 5 mmol, 1 eq.) was added and the mixture was stirred for 16 h.

After ^{1}H-NMR showed complete conversion of the glycidyl ether, all volatiles were evaporated in high vacuum. To a solution of this intermediate (5 mmol) in heptane (10 ml), palmitic acid (1.54 g, 6 mmol, 1.2 eq.) and DMAP (61 mg, 0.5 mmol, 5 mol%) were added, the mixture was chilled to 0 °C and DCC (1.24 g, 6 mmol, 1.2 eq.) was added in one portion. The reaction mixture was stirred for 16 h and subsequently directly placed on a SiO_2 column and chromatographed (Et_2O–pentane = 1 : 10) to afford the desired product (3.24 g, 91%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33–4.87 (m, 1H), 4.33 (dd, J = 11.8, 3.7 Hz, 1H), 4.15 (dd, J = 11.9, 6.3 Hz, 1H), 3.75–3.64 (m, 2H), 2.29 (td, J = 7.6, 2.1 Hz, 4H), 1.68–1.51 (m, 4H), 1.26 (broad s, 57H), 0.94–0.79 (m, 15H), 0.04 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.36, 173.01, 71.64 (–), 62.41, 61.43, 34.31, 34.13, 31.90, 29.68, 29.64, 29.61, 29.46, 29.34, 29.27, 29.11, 29.08, 25.72 (–), 24.92, 24.89, 22.66, 18.16, 14.07, −5.52 (–), −5.56 (–).

$[\alpha]_D$ = +7.1 (c = 2.3, $CHCl_3$).

mp: 45 °C (from pentane–Et_2O).

HRMS: (ESI+) calculated for $C_{43}H_{87}O_5Si$ [M + 1]: 710.624, found: 710.635.

(*R*)-(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-(palmitoyloxy)propyl 10-methyl octadecanoate. A solution of Co[salen] (2.0 mg, 3.32 μmol, 1 mol%) and (*R*)-tuberculostearic acid (100 mg, 335 μmol) in Et_2O (1 ml) was stirred under an oxygen atmosphere (balloon) for 15 min. A change in colour from bright red to red-brown was observed. The solvent was evaporated, and to the resulting brown mixture Hünig's base (58 μl, 335 μmol, 1 eq.) was added, and after 5 min of stirring (*R*)-TBDMS-glycidyl ether (70 μl, 332 μmol, 1 eq.) was added. The resulting mixture was stirred for 16 h after which ^{1}H-NMR showed complete conversion of the glycidyl ether (attenuation of shifts at 2.63 and 2.77). Subsequently, volatiles were evaporated under high vacuum. To the resulting residue were added heptane (800 μl), palmitic acid (102 mg, 398 μmol, 1.2 eq.) and DMAP (2.0 mg, 17 μmol, 5 mol%). After chilling the mixture to 0 °C, DCC (82 mg, 398 μmol, 1.2 eq.) was added in one portion. The mixture was stirred for 16 h and subsequently directly loaded on a SiO_2 column and chromatographed (Et_2O–pentane = 1 : 10) to afford 218 mg (90% over 2 steps) of (*R*)-(*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-(palmitoyloxy)propyl 10-methyloctadecanoate as a colorless thick liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (dd, J = 6.1, 3.7 Hz, 2H), 4.34 (dd, J = 11.8, 3.7 Hz, 2H), 4.16 (dd, J = 11.9, 6.3 Hz, 2H), 3.71 (dd, J = 5.4, 1.0 Hz, 4H), 2.36–2.25 (m, 8H), 1.61 (dd, J = 6.9, 4.9 Hz, 9H), 1.43 (s, 2H), 1.35–0.88 (m, 106H), 0.88–0.80 (m, 28H), 0.09–0.01 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.42 Cq, 173.07 Cq, 71.65 CH, 62.43, 61.44, 37.08, 34.34, 34.15, 32.74 CH, 31.91, 30.02, 29.97, 29.68, 29.64, 29.61, 29.51, 29.46, 29.35, 29.29, 29.27, 29.13, 29.09, 27.07, 27.05, 25.73, 24.93, 24.90, 22.67, 19.68, 18.18, 14.09, −5.49 –$SiCH_3$, −5.54 –$SiCH_3$.

HRMS: calculated for $C_{44}H_{89}O_5Si$ [M + 1]: 725.647, found: 725.649.

$[\alpha]_D$ = +4.5 (c = 1.33, $CHCl_3$).

Synthesis of diacylglycerols. Due to the relative instability of these products, only ^{1}H NMR and ^{13}C NMR (in the first example) were recorded. However, an earlier published study describes[60] characteristic 1,2- and 1,3-diacylglycerol ^{1}H NMR shifts (1,2-diacylglycerol: 3.72 ppm, 5.08 ppm, 1,3-diacylglycerol: 4.05 ppm, 4.21 ppm). For purity see the NMR spectra in the ESI.†

(*S*)-3-Hydroxy-2-(palmitoyloxy)propyl stearate. To a solution of 3-TBDMS protected 1-stearoyl-2-palmitoyl glycerol (1.5 g, 2.1 mmol) in CH_2Cl_2 (20 ml), $CH_3CN{\cdot}BF_3$ (2.0 ml, 1.1 eq.) was added and the resulting light yellow mixture was stirred for 5 min carefully monitored by TLC. After full conversion, the reaction mixture was diluted with Et_2O (100 ml) and poured onto cooled phosphate buffer (1 M, 25 ml). The organic layer was separated and washed with saturated brine (50 ml), dried and evaporated to dryness to afford 1-stearoyl-2-palmitoyl glycerol (1.25 g, 2.1 mmol) as a white solid (99% yield). The compound was used directly without delay and further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12–5.04 (m, 1H), 4.32 (dd, J = 11.9, 4.5 Hz, 1H), 4.23 (dd, J = 11.9, 5.7 Hz, 1H), 3.72 (d, J = 4.9 Hz, 2H), 2.56–2.06 (m, 4H), 1.61 (dd, J = 12.9, 6.8 Hz, 4H), 1.25 (s, 54H), 0.87 (t, J = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.75, 173.40, 72.09 (–), 62.00, 61.51, 34.27, 34.08, 31.90, 29.68, 29.64, 29.60, 29.46, 29.34, 29.25, 29.10, 29.07, 24.92, 24.87, 22.67, 14.09 (–).

(*R*)-(*S*)-3-Hydroxy-2-(palmitoyloxy)propyl 10-methyloctadecanoate. To a solution of (*R*)-(*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-(palmitoyloxy)propyl 10-methyloctadecanoate (81.3 mg, 112 μmol) in CH_2Cl_2 (1 ml), $CH_3CN{\cdot}BF_3$ (100 μl, 123 μmol, 1.1 eq.) was added and the resulting light yellow mixture was stirred for 5 min, carefully monitored by TLC. Upon full conversion, the reaction mixture was diluted with Et_2O (15 ml) and poured onto chilled phosphate buffer (1 M, 5 ml). The organic layer was separated and washed with saturated brine (5 ml), dried and evaporated to dryness to afford (*R*)-(*S*)-3-hydroxy-2-(palmitoyloxy)propyl 10-methyloctadecanoate (65.6 mg, 96%) as a colorless oil. The compound was used directly without delay and further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (m, 1H), 4.32 (m, 1H), 4.26 (s, 1H), 3.75 (s, 1H), 2.34 (dd, J = 15.8, 8.1 Hz, 4H), 2.01 (s, 1H), 1.63 (s, 4H), 1.54 (dd, J = 8.2, 4.9 Hz, 2H), 1.27 (d, J = 8.1 Hz, 47H), 0.94–0.79 (m, 9H).

Major MTB phospholipid precursor

To a stirred solution of 1-(*R*)-TBSA-2-palmitoyl glycerol (63.6 mg, 104 μmol) in CH_2Cl_2 (0.5 ml), phosphoramidite **15** (54.0 mg, 125 μmol, 1.2 eq.) was added. The mixture was cooled to 0 °C and 1*H*-imidazole-4,5-dicarbonitrile (15.4 mg, 0.13 μmol, 1.3 eq.) was added in one portion. The reaction was stirred until complete conversion of the starting diacylglycerol (monitored by TLC – typically 30 min). Subsequently, the mixture was cooled to −20 °C and *t*-BuOOH (*ca.* 5 M in decane, 38 μl, 0.208 mmol) was added, followed by stirring for 30 min. Then the reaction was diluted with 10 ml of CH_2Cl_2 and poured into aqueous $NaHCO_3$ (1 M, 10 ml). The organic layer was washed with aqueous HCl (1 M, 10 ml), brine, dried and evaporated.

The resulting crude yellow oil was purified by column chromatography on SiO_2 ($CHCl_3$–pentane 9 : 1) to afford the desired product (85 mg, 85%) as a colorless thick liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.19 (m, 1H), 5.34 (broad s, 1H), 5.18 (dd, J = 9.6, 5.3 Hz, 1H), 5.11–5.02 (m, 4H), 4.31–4.22 (m, 1H), 4.17–4.01 (m, 4H), 3.42 (m, 2H), 2.32–2.24 (m, 4H), 1.57 (d, J = 7.0 Hz, 4H), 1.46–0.99 (m, 52H), 0.88 (t, J = 6.8 Hz, 6H), 0.83 (d, J = 6.5 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.19, 172.81, 128.80 (–), 128.67 (–), 128.47 (–), 128.09 (–), 128.03 (–), 69.80, 66.78, 65.49, 61.56, 41.33, 37.09, 34.10, 33.97, 32.75 (–), 31.91, 30.02, 29.97, 29.68, 29.64, 29.52, 29.47, 29.35, 29.28, 29.11, 29.06, 27.08, 24.81, 22.67, 19.69 (–), 14.10 (–).

^{31}P NMR (162 MHz, $CDCl_3$) δ −0.81, −0.83.

HRMS: calculated for $C_{55}H_{92}O_{10}NPNa$ [M + Na]: 980.635, found 980.635.

$[\alpha]_D$ = +7.1 (c = 2.3, $CHCl_3$).

All spectral data corresponded to those reported in the literature.[17]

***M. tuberculosis* phospholipid (22).** To a stirred solution of the TBSA lipid precursor (50 mg, 52 μmol) in MeOH/formic acid (2 ml, 96/4), Pd/C (Degussa Type E101 NE/W, 3 mg, 2.6 μmol, 5 mol%) was added. The suspension was stirred under a hydrogen atmosphere (balloon) until complete conversion of the starting material (typically 2 h, according to TLC). Subsequently, the solution was diluted with CH_2Cl_2 (10 ml), and SiO_2 (2 g) was added followed by evaporation of the volatiles. The SiO_2 with adsorbed phospholipid was transferred to a short (5 g) SiO_2 column, impurities were eluted with Et_2O (100 ml) followed by elution of the phospholipid with $CHCl_3$–MeOH–H_2O (65 : 35 : 7) to afford the *M. tuberculosis* phospholipid **22** (32.6 mg, 0.044 mmol, 87%) as a white sticky solid.

^{1}H NMR (400 MHz, C_6D_6) δ 5.19 (s, 1H), 5.07 (s, 1H), 4.36 (d, J = 11.3 Hz, 1H), 4.21–3.80 (m, 4H), 3.64 (s, 4H), 3.37 (s, 1H), 3.09 (s, 1H), 2.27 (dd, J = 15.5, 8.1 Hz, 4H), 1.56 (s, 4H), 1.48–0.98 (m, 44H), 0.98–0.77 (m, 9H).

^{13}C NMR (101 MHz, C_6D_6) δ 173.42, 173.14, 128.41 (–), 127.97 (–), 37.14, 34.24, 34.06, 32.79 (–), 31.92, 30.05, 29.75, 29.70, 29.42, 29.37, 29.25, 27.15, 27.11, 24.94, 24.87, 22.68, 19.65 (–), 14.10 (–).

^{31}P NMR (162 MHz, $CDCl_3$) δ 0.29.

HRMS: calculated for $C_{40}H_{81}NO_8P$ [M + H]: 734.570, found 734.569.

$[\alpha]_D$ = +7.0 (c = 0.3, $CHCl_3$).

Spectral data correspond to those published previously.[17]

Desmethyl analogue of the *M. tuberculosis* phospholipid (14). To a stirred solution of the lipid precursor (50 mg, 52 μmol) in MeOH/formic acid (2 ml, 96/4), Pd/C (Degussa Type E101 NE/W, 2.8 mg, 2.6 μmol) was added. The mixture was stirred under a hydrogen atmosphere (balloon) until complete conversion of the starting material (typically 2 h, according to TLC). Subsequently, the solution was diluted with CH_2Cl_2 (10 ml) and SiO_2 (2 g) was added, followed by evaporation of the volatiles. The SiO_2 with adsorbed phospholipid was transferred to a short (5 g) SiO_2 column, impurities were eluted with Et_2O (100 ml), followed by elution of the phospholipid with $CHCl_3$–MeOH–H_2O (65 : 35 : 7) to afford the desmethyl analogue of the *M. tuberculosis* phospholipid (31.8 mg, 85%) as a white sticky solid.

^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD–D_2O 95/35/2) δ 5.21 (d, J = 4.6 Hz, 1H), 4.38 (dd, J = 12.1, 2.9 Hz, 3H), 4.23 (d, J = 5.3 Hz, 1H), 4.15 (dd, J = 12.1, 7.3 Hz, 1H), 4.02 (t, J = 8.7 Hz, 2H), 3.95 (t, J = 5.9 Hz, 2H), 3.30 (dt, J = 3.2, 1.6 Hz, 1H), 3.19–3.10 (m, 2H), 2.42–2.15 (m, 4H), 1.58 (d, J = 6.6 Hz, 4H), 1.22 (broad s, J = 15.4 Hz, 54H), 0.86 (t, J = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$–CD_3OD–D_2O) δ 174.12, 173.77, 70.38 (–), 63.63, 62.68, 61.56, 34.15, 34.02, 31.83, 29.60, 29.47, 29.45, 29.25, 29.07, 29.03, 24.84, 24.77, 22.56, 13.84 (–).

^{31}P NMR (162 MHz, $CDCl_3$–CD_3OD–D_2O) δ 0.10.

Melting point: 52 °C.

HRMS: calculated for $C_{39}H_{79}NO_8P$ [M + 1]: 720.554, found 720.559.

Synthesis of the platelet-activating factor precursor. In a dry Schlenk flask, hexadecanol (242 mg, 1 eq.) was dissolved in THF (0.4 ml). To this solution, (*R*)-TBDMS-glycidyl ether (390 μl, 0.85 eq.) and Co[salen]OTs catalyst (20 mg, 2.5 mol%) were added. The mixture was stirred for 3 d at rt (progress monitored by GC) until full conversion of hexadecanol. The reaction mixture was diluted with Et_2O (dry, 1 ml), cooled with an ice bath and subsequently DMAP (12.2 mg, 10 mol%), Ac_2O (236 μl, 2 eq.) and Et_3N (350 μl, 2 eq.) were added. The mixture was stirred for 16 h. Et_2O was evaporated, the crude residue was suspended in pentane, transferred to a silica column and chromatographed with 5% Et_2O in pentane to afford 321 mg of **24** (68% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08–4.93 (m, 1H), 3.84–3.64 (m, 2H), 3.64–3.50 (m, 2H), 3.49–3.36 (m, 2H), 2.07 (s, 3H), 1.55 (s, 4H), 1.25 (s, 27H), 0.88 (s, 12H), 0.05 (s, 6H).

The shift at 1.55 ppm overlaps with water from the solvent.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.62, 73.38 (–), 71.72, 68.96, 61.75, 32.06, 29.84, 29.82, 29.80, 29.76, 29.70, 29.60, 29.50, 26.20, 25.91 (–), 25.88, 22.83, 21.29 (–), 18.35, 14.25 (–), −5.31 (–).

HRMS: calculated for $C_{27}H_{57}O_4Si$: 473.401, found 473.402.

$[\alpha]_D$ = +4.0 (c = 1.0, $CHCl_3$).

Platelet-activating factor. In a dry Schlenk tube, PAF precursor **24** (200 mg, 420 μmol) was dissolved in dry CH_2Cl_2 (4.2 ml). This solution was chilled to 0 °C in an ice–water bath and treated with $BF_3{\cdot}CH_3CN$ (240 μl). The reaction was closely monitored in the conversion of **24** (TLC) and after 20 min full conversion was observed. The reaction was quenched by adding cooled phosphate buffer (pH = 7, 1 M). The mixture was diluted with Et_2O (20 ml), the organic layer was washed with water (2 × 10 ml), and brine, dried and evaporated. The crude residue was dried under high vacuum for 30 min and used without further purification (an NMR spectrum was obtained indicating no acyl migration, shifts for ^{1}H NMR: δ 4.99 (m, 1H), 3.82 (m, 2H), 3.68–3.56 (m, 2H), 3.51–3.39 (m, 2H), 2.11 (t, 3H), 1.58–1.53 (m, 30H), 0.88 (t, J = 6.7 Hz, 3H)).

The residue was subsequently dissolved in THF (4.2 ml), and 2-chloro-1,3,2-dioxaphospholan-2-oxide (154 μl, 4 eq.) and Hünig's base (300 μl, 4 eq.) were added. The mixture was stirred overnight (*ca.* 16 h) and as full conversion was observed, the mixture was diluted with Et_2O (25 ml). The organic phase was washed with water, and brine, dried over $MgSO_4$ and evaporated to dryness.

The crude residue was subsequently dissolved in CH_2Cl_2 (1.5 ml), and cooled in an ice/water bath. The solution was treated with TMSOTf (140 μl, 2 equiv., the color changed first to brown and then to red). To this solution Me_3N (55 μl, 1.5 eq.) was added. Since Me_3N is a gas at rt, a syringe wrapped in cotton previously dipped in acetone/liquid N_2 was used. The reaction was monitored by TLC (disappearance of the spot with R_f = 0.21 in Et_2O). Upon full conversion all volatiles were evaporated. The crude residue was transferred to a silica column and carefully chromatographed using a gradient of 1% to 20% MeOH in $CHCl_3$.

149 mg of PAF was obtained as a white waxy solid (68% over 3 steps). NMR spectra of PAF were not indicative due to extensive peak-broadening.

HRMS: calculated for $C_{26}H_{54}NO_7P$ [M + H]: 524.362, found 524.366.

$[\alpha]_D$ = +3.5 (c = 1.0, $CHCl_3$).

Studies on the regioselectivity of the ring-opening and the optical purity of the ring-opened products

TBDPS-(*rac*)-glycidyl ether. In an oven dried Schlenk flask, imidazole (1.58 g, 23.2 mmol, 2.2 eq.) was dissolved in CH_2Cl_2 (5 ml). Neat TBDPSCl (3.4 ml, 1.1 eq.) was added whereupon the mixture turned into a thick suspension which was cooled to 0 °C. To this suspension (*rac*) glycidol (800 μl, 12 mmol) was added. The mixture was stirred for 17 h allowing to reach gradually rt. Solids were filtered and washed with CH_2Cl_2 (3 × 20 ml). The combined organic layers were dried and concentrated. The crude residue was further purified on silica using 20% Et_2O in pentane to yield the desired product in quantitative yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.8 Hz, 2H), 7.41 (m, J = 13.7, 6.8 Hz, 6H), 3.85 (dd, J = 11.9, 3.1 Hz, 1H), 3.71 (dd, J = 11.8, 4.8 Hz, 1H), 3.15–3.10 (m, J = 7.5, 3.8 Hz, 1H), 2.75 (t, J = 4.6 Hz, 1H), 2.61 (dd, J = 5.1, 2.7 Hz, 1H), 1.06 (s, 9H), 0.07 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.94, 135.88 (–), 133.58, 133.57, 130.08, 128.05, 128.04, 64.61 (–), 52.61, 44.77 (–), 27.08, 19.57 (–).

Spectral data are in agreement with those previously published.[61]

TBDPS-(*R*)-glycidyl ether. In an oven dried Schlenk flask, imidazole (295 mg, 2.2 eq.) was dissolved in CH_2Cl_2 (20 ml). Neat TBDPSCl (620 μl, 1.1 eq.) was added whereupon the mixture turned into a thick suspension which was cooled to 0 °C. To this suspension, (*R*)-glycidol (98% ee, 130 μl, 2 mmol) was added. The mixture was stirred for 17 h allowing to reach gradually rt. Solids were filtered and washed with CH_2Cl_2 (3 × 20 ml), and the combined organic layers were dried and concentrated. The crude residue was further purified on silica using 20% Et_2O in pentane to yield the desired product in 86% yield (538 mg, colorless oil).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.8 Hz, 2H), 7.41 (m, J = 13.7, 6.8 Hz, 6H), 3.85 (dd, J = 11.9, 3.1 Hz, 1H), 3.71 (dd, J = 11.8, 4.8 Hz, 1H), 3.15–3.10 (m, J = 7.5, 3.8 Hz, 1H), 2.75 (t, J = 4.6 Hz, 1H), 2.61 (dd, J = 5.1, 2.7 Hz, 1H), 1.06 (s, 9H), 0.07 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.94, 135.88 (–), 133.58, 133.57, 130.08, 128.05, 128.04, 64.61 (–), 52.61, 44.77 (–), 27.08, 19.57 (–).

GC/MS: calculated for $C_{15}H_{15}O_2Si$ [M – ^{t}Bu]: 255, found 255.

Spectral data are in agreement with those previously published.[61]

$[\alpha]_D$ = +2.5 (c = 2.0, $CHCl_3$).

Epoxide ring opening. Reaction for racemic TBDPS-glycidyl ether was performed at the 1 mmol scale using TBDPS-(*rac*)-

glycidyl ether (312 mg, 1 mmol), butyric acid (91.8 mg, 1 mmol), Hünig's base (175 μl, 1 mmol) and of Co[salen] catalyst (10 mol%, 60 mg).

Reaction of enantiopure glycidyl ether was performed on the 0.5 mmol scale using glycidyl ether (156 mg, 0.5 mmol), butyric acid (46 μl, 0.5 mmol), Hünig's base (87 μl, 0.5 mmol) and catalyst (6.0 mg, 1 mol%). Reactions were performed using the following procedure:

A solution of Co[salen] (1 mol%) and butanoic acid (1 eq.) in Et_2O (1 ml) was stirred under an oxygen atmosphere (balloon) for 15 min. A change in color from bright red to red-brown was observed. The solvent was evaporated, and to the resulting brown mixture, Hünig's base (1 eq.) was added, and after 5 min of stirring (*R*)-TBDPS-glycidyl ether (1 eq.) was added. The resulting mixture was stirred for 16 h after which ^{1}H-NMR showed complete conversion of the glycidyl ether (attenuation of the signals at 2.63 ppm and 2.77 ppm). Subsequently, volatiles were evaporated under high vacuum. The crude residue was analysed by HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.7 Hz, 4H), 7.42 (m, 6H), 4.26–4.11 (m, 1H), 3.99–3.90 (m, 1H), 3.88–3.78 (m, 1H), 3.69 (m, 1H), 1.62 (dq, J = 15.0, 7.6 Hz, 2H), 1.06 (s, 9H), 0.93 (t, J = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.15, 135.51, 129.90, 127.81, 70.04, 64.90, 64.40, 35.99, 26.80, 26.72, 19.23, 18.37, 13.65.

HPLC (racemate, c = 1 mg ml^{-1}): CHIRACEL® OD-H, heptane : isopropanol 98 : 2, flow: 1 ml min^{-1}, t_1 = 9.87 min, t_2 = 11.24 min.

HPLC (enantioenriched, c = 1 mg ml^{-1}): t_{major} = 10.03 min, t_{minor} = absent.

MS: calculated for $C_{19}H_{23}O_4Si$ [M – ^{t}Bu]: 343, found 343.

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